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TITLE: **The Use of Quantitative SPECT/CT Imaging to Assess Residual Limb Health**

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CONTRACTING ORGANIZATION: **The Henry M. Jackson Foundation for the Advancement of Military Medicine**
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14. ABSTRACT

The objective of the proposed study is to translate SPECT/CT imaging to patients with lower extremity amputation and subsequently evaluate the utility of non-invasive imaging for evaluating the impact of next-generation socket technologies on the health of the residual limb. It is hypothesized that SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to assess changes in microvascular perfusion elicited by next-generation prosthetic socket technologies and that acute changes in microvascular perfusion will be predictive of long term residual limb health outcomes. While the project timeline is currently slightly behind / delayed from our initial projection, the study team has taken significant actions towards remedying these issues and is very confident that we can get the project back on track in short order and drive towards a successful end point – which will greatly benefit our patients.

15. SUBJECT TERMS
Prosthetics, residual limb health, imaging, extremity trauma, amputation

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INTRODUCTION:

Prosthetic devices aim to restore the appearance and/or function of the affected extremity for patients with amputations. The socket is a critical feature of a prosthetic device as it acts as the interface between the prosthesis and residual limb. Numerous residual limb health issues have been associated with traditional socket technologies. Accordingly, the DoD has invested significant effort and funding in recent years to facilitate the development of improved socket technology to aid in the maintenance of tissue health in the residual limb. While these efforts are beginning to yield exciting next-generation socket technologies (e.g., 'smart' sockets), limited technologies are available to assess the impact of these sockets on the underlying physiological response in the residual limb.

The health of residual limb tissue in persons with lower-limb amputation is of critical importance. Breakdown of tissue viability of the residual limb can negatively impact the progress of the patient's rehabilitation and/or lead to prosthesis abandonment, thus reducing their mobility, function, and overall quality of life. To date, the ability to accurately assess tissue viability within the residual limb of individuals with amputations while the socket is on has been challenging. Therefore, a non-invasive, sensitive, and quantitative imaging modality that could provide an objective assessment of the overall health of the residual limb would advance the standard of care for affected patients, as well as improve selection of the most effective socket technologies at promoting overall limb health.

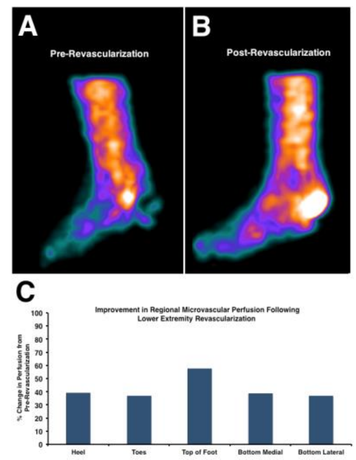


Figure 1. SPECT imaging of a patient with a non-healing heel ulcer before (A) & after (B) revascularization reveals increased microvascular perfusion to the ulcer region & distal foot. Further regional quantification of radiotracer uptake confirmed an improvement in microvascular perfusion in all of the segmented vascular territories of the foot (C).

In accordance with the intent of the FY14 OPORP award mechanism, the goal of the current research study is to provide outcomes data to inform and improve the care of military service members with lower extremity amputation(s). This will be accomplished by utilizing a validated SPECT/CT imaging technique to assess which prosthetic socket technologies will generate the best patient outcomes (i.e., residual limb health) for service members with limb loss. Successful completion of this study would significantly improve our understanding and advance the implementation of the prosthetic socket devices most effective at promoting the overall health of the residual limb, thereby greatly benefiting patient care.

KEYWORDS: Prosthetics, residual limb health, imaging, extremity trauma, amputation

ACCOMPLISHMENTS:

What were the major goals of the project?

The objective of the proposed study is to translate SPECT/CT imaging to patients with lower extremity amputation and subsequently evaluate the utility of non-invasive imaging for evaluating the impact of next-generation socket technologies on the health of the residual limb. It is hypothesized that SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to assess changes in microvascular perfusion elicited by next-generation prosthetic socket technologies and that acute changes in microvascular perfusion will be predictive of long term residual limb health outcomes.

Specific Aim 1 - **To quantify basal microvascular perfusion and perfusion reserve of the residual limb in patients with lower extremity amputation using SPECT/CT imaging.**	**Target Dates** (months)	**Percentage Completion**
Major Task 1: To evaluate SPECT/CT imaging as a means to assess limb health in patients with amputation.		
Subtask 1.1 – WRNMMC IRB Approval	1-6	90%
Subtask 1.2 – Yale University IRB Approval	1-6	100%
Subtask 1.3 – HRPO Approval	1-6	0%
Subtask 1.4 – Human subject testing of SPECT/CT imaging	6-18	0%
Subtask 1.5 – Image analysis and quantification	6-18	0%
Subtask 1.6 – Dissemination of results describing SPECT/CT imaging in an amputee population	18-20	0%
Specific Aim 2 - **To evaluate the efficacy of next-generation (e.g., breathable socket) prosthetic socket technologies at promoting tissue health of the residual limb of patients with lower extremity amputation using SPECT/CT imaging.**	**Target Dates** (months)	**Percentage Completion**
Major Task 2: To use SPECT/CT imaging to evaluate new socket technologies on the long term limb health in patients with amputation.		
Subtask 2.1 – Long term follow up SPECT/CT imaging of 40 subjects	12-22	0%
Subtask 1.5 – Image analysis and quantification of long term follow up imaging	12-22	0%
Subtask 1.6 – Dissemination of results describing use SPECT/CT imaging to evaluate new socket technologies on the long term limb health in patients with amputation.	22-24	0%

What was accomplished under these goals?

During the current reporting period, considerable effort has been devoted towards completion the current project, specifically towards the establishment of the project specific infrastructure:

- The study team has received and responded to numerous stipulations related to the IRB protocol in both administrative (n=3 rounds of questions) and full IRB board review

(n=2 meetings thus far). The team will continue to work with the WRNMMC IRB to get this project fully approved.

- The study team has conducted regular meetings to discuss the project and move it forward.

- A CRADA b/w HJF, WRNMMC, and Yale University is being developed

- Efforts to utilize the WIIR to create digital data collection forms and patient reported outcomes (PROs) are underway. (*note, this technology is being paid for with other leveraged funding (EACE) and thus is at no cost to this project).

- The study team has continued to advertise the position for the HJF research support staff position (which will devote 100% effort toward this project). Dr. Dearth has reviewed numerous applications and interviewed candidates. Several well qualified candidates have been identified, however, an offer has not yet been made due to timing considerations related to getting the IRB approved.

- Efforts were undertaken to initiate the knowledge dissemination process. Specifically, two manuscripts and one abstract on the use of next generation imaging technologies to generate novel, quantitative outcome assessments for the field of O&P have been created, submitted, and accepted by *Advances in Wound Care* and the *Military Health System Research Symposium* (MHSRS) conference, respectively.

What opportunities for training and professional development has the project provided?

This project has provided training and professional development for several of our team members related to regulatory considerations for non-minimal risk studies.

How were the results disseminated to communities of interest?

The general concept of this study – i.e., utilizing next generation imaging technologies to generate novel, quantitative outcome assessments for the field of O&P – have been disseminated to our communities of interest (e.g., Military Medicine) via both manuscripts in peer reviewed, scientific journals and presentations at an internationally renowned conference.

What do you plan to do during the next reporting period to accomplish the goals?

Our main goal for the beginning of the next reporting period is to achieve full regulatory approval (IRB & HRPO) for the clinical protocol such that we can begin subject enrollment. Another goal is to hire the research support personnel for this project – as this individual will be assisting with recruitment, data collection & analysis, etc… we have been mindful to try to synchronize the on-board and regulatory approval dates as closely as possible (i.e., we do not to hire this person 'too soon' [i.e., well before the protocol is approved] such that we do not 'waste' money by having the individual spending down money with nothing to do)

IMPACT:

We expect that this project will significantly improve our understanding and advance the implementation of the prosthetic socket devices most effective at promoting the overall health of the residual limb, thereby greatly benefiting patient care.

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

The project timeline is currently behind our initial projection. This delay was initially due to the issues that were encountered with setting up the sub-award with Yale and associated with changes in the WRNMMC IRB SRC personnel, namely the Chair and Co-Chairs. Additionally, further delays have been incurred due the new online DoD IRB system (iRIS) as well as numerous rounds of revisions requested to the protocol by the WRNMMC IRB.

Importantly, the study team has invested significant efforts towards remedying these issues with the goal of getting the project back on track. We are encouraged in that we have received comments back from the WRNMMC IRB which we addressed and resubmitted such that we can continue to push this effort forward ASAP. Taken together, the study team is very confident that we can get the project back on track during the approved NCE for this project to afford us the opportunity to drive towards a successful end point – which will greatly benefit our patients.

Changes that had a significant impact on expenditures

Nothing to Report.

Expenditures are significantly less than originally budgeted at this point in the study.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report.

PRODUCTS:

Journal publications.

The study team contributed manuscripts to a special issue of *Advances in Wound Care* which is dedicated to “Amputee Care and Rehabilitation”. The focus of these knowledge products was that of this funded project – i.e., highlighting the importance of advanced imaging modalities in evaluating residual limb health of service members and veterans with limb loss. The citation for this knowledge product is listed below and the full length articles included in the appendix.

- **Mitchel R. Stacy** and **Christopher L. Dearth**. "*Multimodality imaging approaches for evaluating traumatic extremity injuries: implications for military medicine*". Adv Wound Care (New Rochelle). 2017 Jul 1;6(7):241-251. doi: 10.1089/wound.2016.0716.

- Courtney Butowicz, **Christopher L. Dearth**, Brad D. Hendershot. "*Impact of traumatic lower extremity injuries beyond acute care: Movement-based considerations for resultant long-term secondary health conditions*". Adv Wound Care (New Rochelle). 2017 Aug 1;6(8):269-278. doi: 10.1089/wound.2016.0714.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers, and presentations.

The study team contributed an abstract to the 2017 Military Health System Research Symposium (MHSRS) conference. The focus of these knowledge products was that of this funded project – i.e., highlighting the importance of advanced imaging modalities in evaluating residual limb health of service members and veterans with limb loss. The citation for this knowledge product is listed below and the full length abstract and poster are included in the appendix.

- **Mitchel R. Stacy** and **Christopher L. Dearth**. "*Evaluating Traumatic Extremity Injuries Using Multimodality Imaging: Emphasis on SPECT/CT Imaging and Implications for Military Medicine*".Military Health System Research Symposium (MHSRS) Conference, Kissimmee, FL 2017.

Website(s) or other Internet site(s)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Christopher L. Dearth, PhD
Project Role:	Principle Investigator
Name:	Mitchel R. Stacy, PhD
Project Role:	Co-Principle Investigator

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report. No changes have been made to efforts on this project.

What other organizations were involved as partners?

No new organizations were involved as partners

SPECIAL REPORTING REQUIREMENTS

QUAD CHART:

(See next page)

The Use of Quantitative SPECT/CT Imaging to Assess Residual Limb Health

Orthotics and Prosthetics Outcomes Research Award - W81XWH-15-1-0669

PI: Christopher L. Dearth, PhD **Org:** Walter Reed National Military Medical Center **Award Amount:** $484,210

Objective: The objective of the proposed proof of concept, pilot clinical study is to translate ^{99m}Tc-tetrofosmin SPECT/CT imaging to patients with lower extremity amputation and subsequently evaluate its effectiveness as a means to evaluate the impact of next generation socket technologies on the health of the residual limb. This objective will be evaluated by the following specific aims:

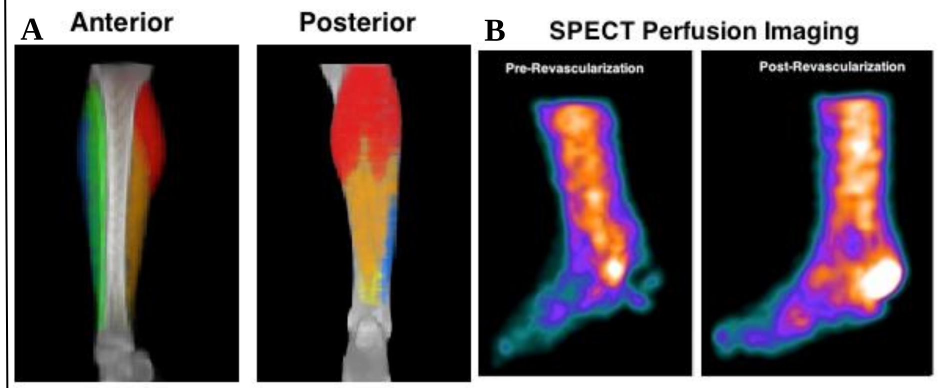
Specific Aim 1: To quantify basal microvascular perfusion and perfusion reserve of the residual limb in patients with lower extremity amputation using ^{99m}Tc-tetrofosmin SPECT/CT imaging.

Hypothesis: It is hypothesized that evaluation of microvascular perfusion via ^{99m}Tc-tetrofosmin SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to use during the assessment of residual limb tissue health beyond traditional limb health outcome measures.

Specific Aim 2: To evaluate the efficacy of current (e.g., VASS) and next-generation (e.g., breathable socket) prosthetic socket technologies at promoting tissue health of the residual limb of patients with lower extremity amputation using ^{99m}Tc-tetrofosmin SPECT/CT imaging.

Sub Aim 2.1 - To determine if acute changes in microvascular perfusion are predictive of long term residual limb health outcomes.

Hypothesis: It is hypothesized that ^{99m}Tc-tetrofosmin SPECT/CT imaging will provide a highly sensitive, non-invasive tool for clinicians to assess changes in microvascular perfusion elicited by next-generation prosthetic socket technologies and these acute changes in microvascular perfusion will be predictive of long term residual limb health outcomes.



A) Anterior & posterior views of 3-D calf muscle regions segmented from a CT attenuation scan. Gastrocnemius (red), soleus (orange), tibialis anterior (green), tibialis posterior (yellow), and fibularis longus (blue) muscles are displayed and overlaid on a bone only CT image. **B**) ^{99m}Tc-tetrofosmin SPECT perfusion imaging in a patient with a non-healing heel ulcer prior to and following lower extremity revascularization demonstrates increased radiotracer uptake in the site of the heel ulcer and distal foot following treatment.

Timeline and Cost

Activities **Calendar Year** (Funding Year)	**2016** (1)	**2017** (2)	**2018** (NCE)
IRB creation / submission / approval			
Begin subject recruitment / enrollment			
Specific Aim #1			
Specific Aim #2			
Study Completion / Data Dissemination			
Budget ($K)		**$244**	**$240**

Goals / Milestones

CY16 Goals – Initiation / IRB / Personnel

- ☑ Study kickoff meeting
- ☑ Clinical research protocol generation
- ☑ Generation of position description for research personnel

CY76 Goal – Study Initiation / Data Collection

- ☑ WRNMMC IRB SRC submission
- ☐ Full WRNMMC IRB Approval
- ☐ Begin subject recruitment / enrollment
- ☐ Begin data collection for SA 1 & 2

CY18 Goal – Study Completion

- ☐ Complete data collection for SA 1 & 2
- ☐ Manuscript(s) submission / publication
- ☐ Conference abstract submission / presentation

Updated: 30 Oct 2017

CRITICAL REVIEW

Multimodality Imaging Approaches for Evaluating Traumatic Extremity Injuries: Implications for Military Medicine

Mitchel R. Stacy[1,*] and Christopher L. Dearth[2–4]

[1]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.
[2]DOD-VA Extremity Trauma and Amputation Center of Excellence, Walter Reed National Military Medical Center, Bethesda, Maryland.
[3]Research and Development Section, Department of Rehabilitation, Walter Reed National Military Medical Center, Bethesda, Maryland.
[4]Regenerative Biosciences Laboratory, Department of Rehabilitation Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Mitchel R. Stacy, PhD

Submitted for publication November 1, 2016.
Accepted in revised form December 22, 2016.
*Correspondence: Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, Dana 3, P.O. Box 208017, New Haven, CT 06520-8017 (e-mail: mitchel.stacy@yale.edu).

Significance: Military service members are susceptible to traumatic extremity injuries that often result in limb loss. Tremendous efforts have been made to improve medical treatment that supports residual limb function and health. Despite recent improvements in treatment and novel prosthetic devices, many patients experience a wide range of clinical problems within residual limbs that can negatively impact the progress of rehabilitation programs while also impairing functional capacity and overall quality of life.
Recent Advances: In addition to existing standard imaging modalities that are used for clinical evaluation of patients suffering from traumatic extremity injury, novel noninvasive imaging techniques are in development that may facilitate rapid and sensitive assessment of various aspects of traumatic extremity injuries and residual limb health.
Critical Issues: Despite recent advances, there remains a clinical need for noninvasive quantitative imaging techniques that are capable of providing rapid objective assessments of residual limb health at the time of initial presentation as well as after various forms of medical treatment.
Future Directions: Ongoing development of imaging techniques that allow for assessment of anatomical and physiological characteristics of extremities exposed to traumatic injury should greatly enhance the quality of patient care and assist in optimizing clinical outcomes.

Keywords: imaging, extremity trauma, amputation, military medicine

SCOPE AND SIGNIFICANCE

The following review discusses a variety of imaging modalities that are currently available and used clinically for assessing traumatic extremity injuries, while also addressing relative benefits and limitations associated with each modality. In addition, several imaging modalities that have been more recently developed and are in the process of validation are discussed in the context of evaluating patients with traumatic extremity injuries.

TRANSLATIONAL RELEVANCE

A variety of noninvasive imaging techniques that could have potential application in the assessment of traumatic extremity injuries con-

DOI: 10.1089/wound.2016.0716

tinue to be developed and validated in the preclinical setting. Numerous animal models of limb ischemia and skeletal muscle tissue injury are available for initial testing; however, before obtaining FDA approval and widespread clinical application, these imaging modalities must undergo rigorous testing and validation. Ongoing efforts by imaging scientists should facilitate the development of noninvasive quantitative indices that will one day assist clinicians with improved assessment and tracking of medical treatments in patients suffering from traumatic extremity injuries.

CLINICAL RELEVANCE

Advances in protective body armor, vehicles, and medical treatment have improved combat survival rates; however, survivors often suffer traumatic extremity injuries.[1,2] As of October 1, 2016, there are 1,703 service members who have sustained traumatic limb loss due to Operations: Enduring Freedom, Iraqi Freedom, New Dawn, Inherent Resolve, and Freedom's Sentinel (Source: Extremity Trauma and Amputation Center of Excellence, Walter Reed National Military Medical Center). Though less apparent, the civilian population also suffers from traumatic extremity injuries; an estimated 185,000 Americans undergo limb amputation annually,[3] and an estimated 900,000 will be living with traumatic limb loss in 2020.[4]

BACKGROUND

The integrity of the vasculature, nerves, and soft tissue within the extremities is of high importance, as an impairment or deficiency to any of these tissues in isolation or combination can lead to issues with residual limb pain, impair the progress of rehabilitation programs, and/or result in prosthesis abandonment, thus reducing mobility, function, and overall quality of life for patients.[5] Residual limb pain, in particular, may occur due to numerous reasons, such as neuroma, chronic inflammation, infection, retained foreign bodies, heterotrophic bone formation, and vascular abnormalities.[6] Therefore, effective diagnosis can be critical in directing the medical treatment of patients. Standard noninvasive imaging modalities such as ultrasound, X-ray computed tomography (CT) imaging, magnetic resonance (MR) imaging, single photon emission computed tomography (SPECT), and positron emission tomography (PET) are currently available for assessing various aspects of extremity health. Specifically, X-rays, CT, and MR are used for imaging suspected anatomical complications associated with extremity trauma, such as vascular (*e.g.*, pseudoaneurysm, vascular stenosis or occlusion, hematoma) and nonvascular injuries (*e.g.*, bone fracture, soft tissue defect or trauma). Alternatively, SPECT and PET are the primary modalities for physiological imaging of molecular and cellular processes (*e.g.*, inflammation, metabolism, angiogenesis). However, with the development of hybrid systems such as SPECT/CT, PET/CT, and PET/MR, clinicians can now co-register anatomical images with functional images. Despite the breadth of currently available modalities, all clinical imaging modalities possess relative benefits and limitations related to their ability to provide comprehensive noninvasive assessment of extremity health (Table 1). Other imaging modalities are still in developmental stages and have yet to be validated as clinically useful tools; however, recently, there has been an increased focus on the development of noninvasive imaging approaches that are capable of assessing tissue viability in patients with limb loss. The ability to assess tissue viability through the evaluation of vascular supply as well as tissue blood flow, perfusion, and/or oxygenation within residual limbs could provide novel insight into physiological changes that occur after surgical or medical treatment while also allowing for improved assessment of next-generation prosthetic devices. Therefore, sensitive, quantitative imaging approaches that could provide an objective assessment of residual limb health should have increased roles in the future and advance the standard of care for patients suffering from traumatic extremity injuries and extremity amputation.

ULTRASOUND

Within the clinical setting, ultrasound is one of the most frequently used imaging modalities due to its relatively low cost and easy portability. Ultrasound systems utilize the principle of wave reflection and echo from oscillating sound waves in tissues to produce two-dimensional (2D) and three-dimensional (3D) real-time images of structure, function, and blood flow, thus making this modality particularly relevant and valuable as a tool for

Table 1. *Characteristics of imaging modalities available for assessing extremity trauma*

Modality	*Sensitivity*	*Penetration Depth*	*Spatial Resolution*
Ultrasound	Moderate	Low	1 mm
CT imaging	Limited	No limit	<1 mm^3
MR imaging	Moderate	No limit	<1–3 mm^3
SPECT	High	No limit	~ 5–8 mm^3
PET	High	No limit	~ 3–5 mm^3

Modified from Stacy and Sinusas.[7]

CT, computed tomography; MR, magnetic resonance; PET, positron emission tomography; SPECT, single photon emission computed tomography.

quick, noninvasive assessment of a variety of injuries associated with extremity trauma.[7]

In patients who have experienced traumatic lower extremity injuries and undergone amputation, ultrasound imaging has been shown to be a valuable tool for assessing nerve-related complications.[6,8–10] Specifically, ultrasound has been shown to be useful for visualizing sciatic nerves and residual limb neuromas, which are caused by growing proximal axons from the amputated nerve that lead to the formation of painful bulbous overgrowths.[9] Neuromas represent a frequent cause of residual limb pain after amputation and appear on ultrasound images as oval, hypoechoic masses that are in contact with the nerve.[11] Due to the relationship between the nerve and neuroma, ultrasound imaging along the path of the nerve can be used to localize the source of pain for guidance of fine needle aspiration or biopsy. In addition, ultrasound imaging of neuromas has been shown to allow for real-time guidance of various treatments, including local anesthetic injections with and without steroids, neurolytic injections, radiofrequency ablation, and surgical revision.[6,8,9] Figure 1 demonstrates the value of ultrasound imaging of a neuroma before and after treatment with a steroid anesthetic mixture, where the needle placement is visualized in real time for guidance of the therapeutic injection.[8] In addition to image guidance for treatment of neuromas, color flow Doppler ultrasound has also been shown to be useful for visualization of vascularity around the site of neuroma formation, thus adding further value to ultrasound by allowing clinicians to avoid specific vascular structures during therapeutic injections, as well as permitting evaluation of the relationship between various therapies and associated changes in neuroma blood flow and pain.[6]

Along with assessing residual limb neuromas, ultrasound imaging has been found to be a useful tool for evaluating structural changes that occur in the patellar tendon of patients with traumatic transtibial amputations.[12] Since the patellar tendon can be a significant weight-bearing structure for prosthetic use in individuals with transtibial limb loss, ultrasound can possess significant value for designing prosthetic devices that allow for optimal load transfer between the prosthesis and residual limb. Indeed, prior work has already demonstrated that ultrasound is capable of assisting in the development of prosthetic sockets through the measurement and modeling of the residual limb-to-prosthetic socket interface.[13] Improved assessment and understanding of the complex biomechanical interactions between the residual limb and prosthetic socket should allow for improved next-generation designs that facilitate optimal pressure distribution over the residual limb. Research in the field of finite element analysis has shown that ultrasound imaging can be useful for modeling of the limb-to-socket interface by developing quantitative indices to predict the quality of prosthetic fit. This finite element modeling of the limb-to-socket interface is critical not only at the time of prosthetic development but also over time, as residual limbs can undergo serial changes due to muscle atrophy, edema, and weight gain or loss, among others.[13] Any of these changes in residual limb structure and health can contribute to the future development of limb pain or skin

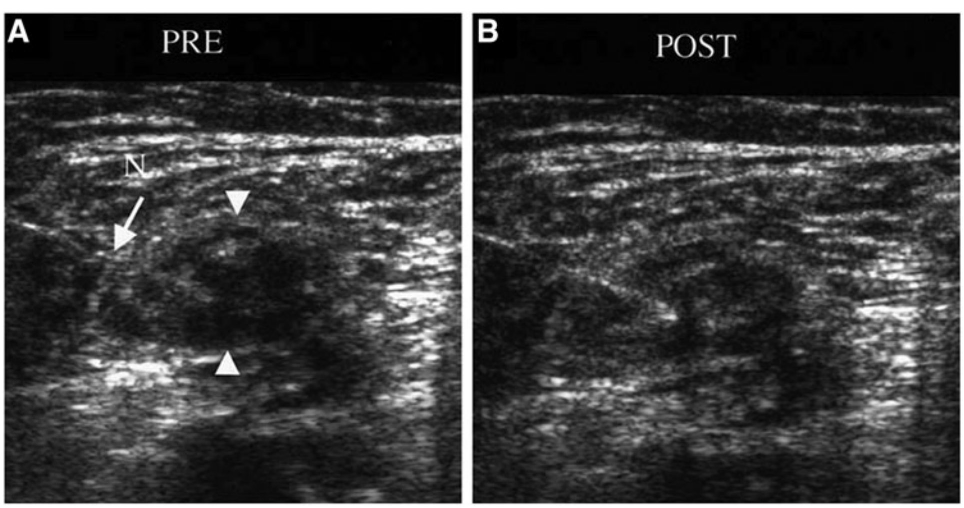


Figure 1. Ultrasound imaging of a neuroma with the needle in position **(A)** before and **(B)** after anesthetic steroid injection (*arrowheads* represent location of neuroma; *arrow* denotes location of needle). **(B)** After the injection, increased echogenicity is noticed within the neuroma, demonstrating effective delivery of the steroid anesthetic. Reprinted with permission from Ernberg *et al.*[8] N, needle.

damage. Therefore, the use of ultrasound imaging to precisely model and predict changes in residual limb characteristics should facilitate future efforts that are directed at optimizing limb-to-socket fitting while also improving the long-term outlook for patients with lower extremity limb loss.

In addition to being a useful noninvasive tool for assessing the lower extremities, ultrasound imaging has been extensively applied in the evaluation of traumatic upper extremity injuries. In the setting of traumatic extremity injury, ultrasound has been utilized to assess tendons, peripheral nerves, vascular structures, bone fractures, and foreign bodies.[14] For tendon-specific injuries, ultrasound can identify partial or full tendon rupture, swelling, and effusion in the tendon sheath. In addition, ultrasound imaging can be applied to noninvasively assess superficial peripheral nerves and identify damage to their normal fasicular pattern, nerve swelling or thickening, loss of nerve bundle integrity, and development of neuromas. Due to the superficial location of some upper extremity peripheral nerves, ultrasound can be applied for quick noninvasive assessment after traumatic injury, therefore assisting in diagnosis of nerve injuries that necessitate immediate surgical repair. Along with nerves, vessels of the upper extremities are susceptible to traumatic injury due to their tendency to be superficial and/or close to the bone,[15] with penetrating trauma being the most frequent cause of traumatic upper extremity vascular injury.[16] In instances of traumatic vascular injury, ultrasound can be extremely useful for evaluating the patency of the affected artery or vein as well as the integrity of the vascular wall.[14] Although potential bone fractures are commonly assessed and identified by using standard radiography, CT imaging, or MR imaging, superficial bones of the upper extremities can also be identified by using ultrasound imaging and can provide an alternative approach for quick assessment of traumatic bone and joint injuries.[17]

One of the most relevant applications of ultrasound for military medicine can be in the identification of foreign bodies following instances of penetrating wounds, which can result in pain and tissue infection. Since ultrasound allows for identification of both opaque and radiolucent foreign bodies, this modality offers some advantages over standard radiography, which can only identify radiopaque materials.[18] Fast and accurate identification of foreign bodies can be critical for directing surgical removal and can provide the anatomical location of the foreign body in relation to tendons, nerves, and vessels.[14] In addition to providing the location of the foreign body, ultrasound imaging can also assist in characterizing wound tracts after traumatic extremity injuries such as soft tissue gunshot wounds.[19]

X-RAY AND CT IMAGING

In the setting of traumatic extremity injury, digital subtraction angiography (DSA) and CT angiography have been the imaging modalities of choice for evaluating patients with possible vascular injuries. Traditionally, DSA was the primary imaging approach for evaluating vascular integrity after traumatic extremity injury; however, the development of modern-day CT scanners has resulted in rapid image acquisition times and whole-body imaging that possesses high accuracy and excellent penetration depth at sub-millimeter isovolumetric voxels, therefore offering high spatial resolution of vascular anatomy, bone, and surrounding soft tissue.[20,21] Although CT imaging requires the use of X-rays and exposes patients to ionizing radiation,[7] many CT scanners now possess the ability to modulate radiation exposure to patients through various attenuation-based techniques.[20] CT imaging has become such a vital component of clinical care for patients with traumatic injuries that we have now reached an era where almost every emergency department has at least one CT scanner available at any given time.[22]

In the evaluation of patients exposed to blast injuries, both X-ray and CT imaging are fast and effective imaging techniques that are capable of detecting bone fractures. In addition, metallic and/or glass fragments, which possess a higher relative density than soft tissue, can be identified as radiopaque objects in the extremities after traumatic injury.[23] No matter the cause of traumatic injury (*e.g.*, blast injury, stab wound, or gunshot wound), CT imaging on 16- and 64-slice scanners offer unique opportunities to have the combination of high spatial and temporal resolution, along with fast image reconstruction and data processing techniques, all of which are critical in the emergency diagnosis and surgical planning for patients suffering from traumatic injury.[22]

Although CT imaging provides value in the noninvasive assessment of bone, soft tissue defects, and fragments in soft tissue after extremity trauma (Fig. 2), an important capability of CT imaging remains the rapid assessment of vascular structures, since vascular injuries significantly contribute to morbidity and mortality associated with traumatic injuries.[20] In patients with suspected vascular injuries, CT angiography is the initial modality of choice and has been shown to have high

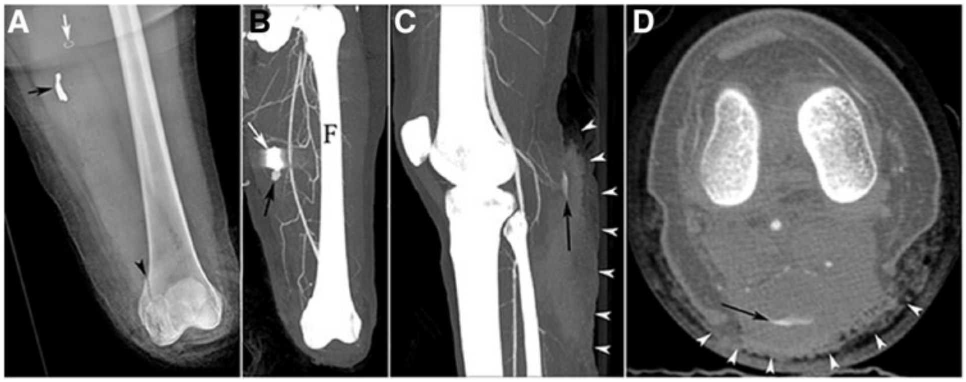


Figure 2. CT imaging in a patient after primary and secondary blast injuries to the lower extremities and an emergency below-the-knee amputation of the left limb. **(A)** Radiography postamputation identified the presence of a metallic foreign body (*black arrow*), surgical staple (*white arrow*), and distal femoral fracture (*arrowhead*) in the left limb. **(B)** A maximum intensity projection (MIP) of CT angiography revealed a pseudoaneurysm (*black arrow*) in the immediate proximity of shrapnel (*white arrow*). **(C)** A sagittal MIP of a CT angiogram of the right limb identified the presence of a second pseudoaneurysm (*black arrow*) that is also apparent in the **(D)** axial view, in combination with a prominent soft tissue defect on the posterior aspect of the limb (*arrowheads*). Reprinted with permission from Guermazi *et al.*[23] CT, computed tomography; F, femur.

sensitivity and specificity for diagnosis of extremity vascular injuries.[24,25] Specifically, Soto *et al.*[26] demonstrated a sensitivity of 95.1% and specificity of 98.7% when applying CT angiography for the detection of focal arterial injuries in patients suffering from penetrating and blunt traumatic injuries, whereas Rieger *et al.*[21] found that CT angiography had 95% sensitivity and 87% specificity for detection of peripheral vascular lesions. Recent research also suggests that CT angiography predicts limb salvage rates in patients suffering from lower extremity vascular injury, where the need for surgical intervention and amputations was found to increase as the number of patent vessels to the lower extremity decreased.[27] Direct evidence of vascular injury on CT angiography can be indicated by extravasation of the intravenous iodinated contrast agent, localization of extraluminal contrast (suggestive of pseudoaneurysm), vascular stenosis or occlusion, or arteriovenous fistulae, whereas more indirect evidence of vascular injury may appear as a perivascular hematoma or a projectile in close proximity to an artery.[28] In instances when CT angiography findings are inconclusive, as in cases of potential vascular dissection, patients may require conventional DSA under fluoroscopic guidance to assist with diagnosis and guidance of endovascular treatment or surgical planning.[29] Specific vascular injuries that may be better identified by secondary inspection on DSA include vascular dissection, occlusion, and spasm. Aside from instances when significant CT image artifacts are anticipated due to metallic shrapnel from blast injuries or gunshot wounds, DSA remains a second-line tool to CT angiography for the noninvasive assessment of vascular injuries at a majority of trauma centers.[20]

Despite the numerous advantages that CT angiography and DSA provide in the noninvasive evaluation of extremity trauma, there are also limitations that exist for both modalities. Two primary limitations of DSA and CT imaging unrelated to image quality include the use of X-rays that emit ionizing radiation that is capable of damaging DNA, and the use of iodinated contrast agents that can be nephrotoxic for patients with impaired renal function.[7] Additional pitfalls associated with CT image quality in trauma patients include metal fragments and other foreign objects associated with trauma that can produce high attenuation image artifacts that prevent visualization of specific vessel segments.[22] Therefore, radiologists should carefully review cross-sectional images to optimize evaluation of vascular injuries that are not be as readily detected on 3D-rendered images due to metallic streak artifacts, motion artifacts, and nonenhanced vascular segments.[28]

MR IMAGING

MR imaging utilizes magnetic fields of varying strengths (1.5–9.4 Tesla for human use and greater than 10 Tesla for research purposes) to send and receive radio frequency pulse sequences that produce high-resolution images that are capable of assessing anatomy and physiology without the need for ionizing radiation. Since MR possesses good penetration depth, superior soft tissue contrast, and does not require ionizing radiation, this imaging modality has been widely applied for evaluating anatomical and functional characteristics of the extremities.[7] However, despite the recognized advantages of MR imaging, MR is not

indicated in the acute stages of trauma after blast injury due to the likelihood of metallic foreign bodies being present in the body, as well as the length of time required for acquisition of MR images compared to CT imaging. In addition, MR imaging is more expensive than ultrasound and CT imaging and, therefore, not always as readily available as an initial tool for diagnosing complications associated with blast trauma.[23]

In instances of extremity trauma not associated with blast injury, MR imaging is becoming a preferred modality for assessing injuries to extremity soft tissue. In particular, MR imaging is a valuable noninvasive tool for identifying and characterizing the extent of neural injuries and nerve impairment, as well as associated issues such as muscle edema and denervation (Fig. 3).[30] Extremity trauma can result in neuropathy due to direct injury to nerves, or from injury to adjacent anatomical structures. High-resolution 2D fast spin echo sequences are one MR-based approach that can be utilized to detect numerous nerve-related injuries in the extremities, such as traumatic or iatrogenic injuries, nerve entrapment, inflammation, and tumor-like lesions.[30] In addition, volumetric MR imaging has been shown to be a useful tool for quantifying sensory neuron loss within dorsal root ganglia after nerve transection.[31] A more recent emerging tool for assessment of peripheral nerves is 3D diffusion tensor imaging (DTI) with MR tractography, which allows for visualization of nerve orientation and course.[32] DTI permits visualization of nerve tractography and microstructural characteristics by utilizing the anisotropic diffusion of water molecules through axons, thereby producing quantifiable parameters (*e.g.*, fractional anisotropy, mean diffusivity, eigenvalues) that offer insight into characteristics such as axon density and myelin thickness.[33,34] DTI-derived measures of fractional anisotropy have been shown to correlate well with histological analyses of axons and myelin[35] while also demonstrating the ability to noninvasively identify serial changes in nerve characteristics after peripheral nerve injury in patients[36] and animal models.[34,35,37,38] Collectively, MR-based imaging of peripheral nerves possesses significant clinical potential as a tool for quantitatively assessing the effects of microsurgical repair of nerves as well as neuroprotective therapies after extremity trauma.

Along with established techniques for assessing extremity nerves, MR imaging has also demonstrated utility in characterizing numerous other extremity complications, including neuromas, bursitis, soft tissue inflammation, abscesses, osteomyelitis, stress fractures, bone bruises, cutaneous lesions, and neoplastic recurrences.[39] In patients who undergo amputation of a limb, MR imaging is particularly useful for identifying bursitis, adventitious bursae, and regions of localized soft tissue inflammation, resulting from an improper interaction between the residual limb stump and prosthetic device. In the noninvasive diagnosis of residual limb stump bursitis, MR assists in differentiating inflammation between cutaneous and subcutaneous tissue, as well as identifies differences between bone and muscle inflammation caused by abnormal levels of mechanical stress on the residual limb.[40] In addition to an evaluation of structural and inflammatory consequences associated with improper socket fitting, nuclear MR spectroscopy has also been applied in patients with lower extremity amputation to assess exercise-induced changes in skeletal muscle

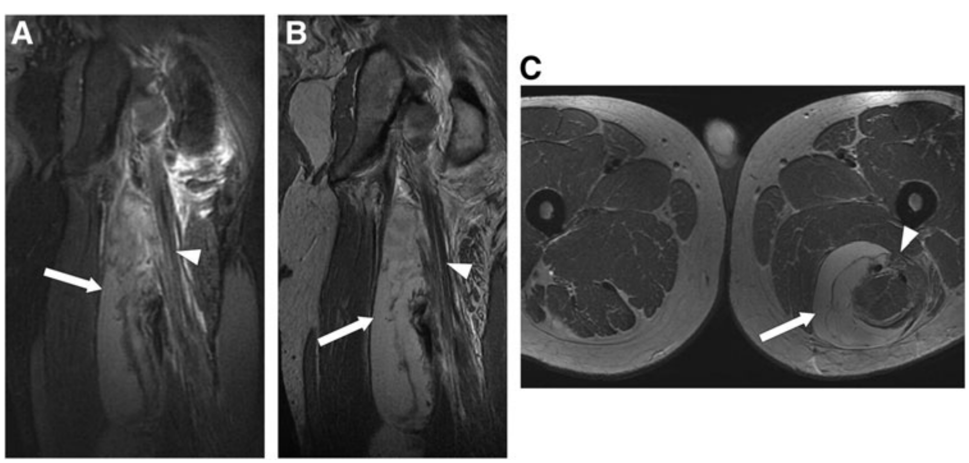


Figure 3. **(A)** Coronal views of inversion recovery and **(B)** fast spin echo, as well as **(C)** axial view of fast spin echo MR images after traumatic injury to the lower extremities reveal the presence of a large hematoma (*white arrow*) that is responsible for compression of the left sciatic nerve (*white arrowheads*). Reprinted with permission from Burge *et al.*[30] MR, magnetic resonance.

metabolism, demonstrating further applicability and relevance of MR-based approaches in the assessment of patients after traumatic extremity injury and limb loss.[41]

In the assessment of vascular abnormalities in the extremities, multiple MR angiography approaches are available that do not require the use of iodinated or gadolinium-based contrast agents, which is particularly valuable in assessing patients with renal insufficiency. Specifically, time-of-flight and phase-contrast imaging are capable of producing dynamic images of blood vessels, but are limited in their application in extremity trauma due to long acquisition times and their tendency to overestimate vessel stenosis.[42] More recent MR techniques such as quiescent-interval single-shot MR angiography, cardiac-gated 3D-fast spin echo MR angiography, and flow-sensitive dephasing sequences have been developed that allow for relatively faster acquisition times, and they are capable of producing diagnostic-level images that possess similar sensitivity as contrast-enhanced MR angiography.[43,44] In addition to noncontrast approaches, contrast-enhanced MR angiography with gadolinium-based contrast agents remains a viable option that produces fast, dynamic, and high-temporal resolution angiographic images, which is valuable in the setting of extremity trauma by allowing for differentiation of high-flow and low-flow vascular abnormalities.[28]

Aside from assisting with diagnosis of complications associated with extremity trauma, MR imaging has also proved to be a useful tool for evaluating the prosthesis-to-residual limb interface and has been utilized to identify extremity characteristics for modification and optimization of prosthetic device fit. Specifically, Douglas *et al.*[45] previously developed algorithms that allow for the automatic extraction of the skin and bone boundaries from MR images of individuals with lower extremity limb loss to facilitate biomechanical modeling (*i.e.*, finite element analysis) of the residual limb-to-prosthetic interactions, whereas additional work by Buis *et al.*[46] has used MR images to establish a reference grid of residual limbs to quantify differences in volume and shape of soft tissues. Taken together, this information related to the residual limb could provide valuable information to guide individualized design of prosthetic devices that allow for ideal comfort and optimize patient mobility.

RADIOTRACER IMAGING

SPECT and PET imaging are the standard clinical imaging modalities for radiotracer-based imaging that allows for high-sensitivity 3D assessment of a wide range of physiological processes via detection of gamma rays and photons emitted from the radioactive decay of isotopes. Though SPECT and PET provide high-sensitivity functional images, both offer low spatial resolution and are, therefore, typically paired with high-resolution anatomical images produced by CT or MR systems for accurate radiotracer localization and quantification. In addition, both SPECT and PET imaging expose patients to ionizing radiation due to the use of isotopes that possess varying half-lives.[7]

SPECT/CT imaging has been applied in the clinical environment for many years for the assessment of myocardial perfusion in patients with coronary artery disease; however, SPECT/CT may also have value in the assessment of extremity trauma through its ability to evaluate skeletal muscle perfusion under conditions of rest or stress.[47] In addition, SPECT/CT imaging has already demonstrated potential for assessing a wide range of other physiological processes, such as bone and tissue infection,[48–51] heterotrophic ossification,[52] and skeletal muscle angiogenesis,[47] which could be useful in the evaluation of extremity trauma and tracking the response to medical treatment. In the assessment of infection, multiple technetium-99 m (^{99m}Tc)-labeled radiotracers have been applied in the extremities. Specifically, Filippi and Schillaci[50] utilized ^{99m}Tc-hexamethylpropylene amine oxime-labeled leukocytes to localize and define the extent of infection in patients with suspected osteomyelitis and joint infections, whereas Erdman *et al.*[51] have applied ^{99m}Tc-labeled white blood cells to assess infections and developed a standardized scoring system for rating the severity of wound infections. In addition, ^{99m}Tc-hydroxydiphosphonate SPECT/CT imaging has been utilized to evaluate painful knee prostheses and has demonstrated the ability to identify instances of prosthesis loosening or associated tissue infection.[49] Aside from SPECT/CT imaging of infection, ^{99m}Tc-methyl diphosphonate (MDP)[53] as well as gallium-67 (^{67}Ga) citrate[48] have been applied in instances of suspected osteomyelitis of the extremities, and ^{99m}Tc-MDP has been used for the additional noninvasive identification of heterotrophic ossification at the site of residual limb stumps.[52]

In addition to potential clinical applications of SPECT/CT imaging in the noninvasive assessment of extremity trauma, PET/CT imaging also possesses capabilities that could have considerable value in patients. Specifically, a frequently used PET tracer, fluorine-18 (^{18}F)-fluorodeoxyglucose (FDG), has been applied in the assessment of suspected osteomyelitis and demonstrated excellent sensitivity (100%), specificity (93%), and accuracy

(96%) in a lesion-based analysis.[54] ^{18}F-FDG PET/CT imaging has also shown value for assessing exercising skeletal muscle metabolism in the lower extremities of patients with transfemoral amputation by characterizing variations in metabolic activity between specific muscle groups of the lower extremities, indicating potential utility of FDG imaging in the evaluation of patients undergoing exercise rehabilitation programs.[55] Along with imaging of muscle metabolism, FDG PET imaging has also been paired with high-resolution anatomical MR imaging to noninvasively assess metabolic activity within peripheral nerves and has demonstrated increased radiotracer uptake within injured sciatic nerves (Fig. 4).[56] In addition to FDG PET/CT imaging, PET imaging with oxygen-15 (^{15}O)-water has proved to be useful for quantifying muscle blood flow and identifying areas of tissue ischemia with sensitivity and specificity levels similar to those of laser Doppler imaging and transcutaneous oxygen ($TcPO_2$) measurements, leading the authors to suggest that quantitative PET imaging could be useful for future assessment of lower extremity tissue viability and in determining the appropriate level of amputation before surgical intervention.[57]

Although both SPECT and PET imaging have demonstrated efficacy for evaluating skeletal muscle perfusion and blood flow, both imaging approaches have relative benefits and limitations, and thus one modality may be more favorable depending on the clinical scenario. For example, SPECT is performed by using radioisotopes that possess longer half-lives, which can be beneficial when combining lower extremity perfusion imaging with clinically indicated myocardial perfusion imaging. However, longer half-life tracers can be unfavorable due to the resultant higher doses of ionizing radiation for patients. SPECT imaging is more widely available than PET due to higher costs associated with PET imaging, which remains costly for medical centers due to the need for more expensive instrumentation, including an onsite cyclotron or portable generator for isotope production. PET scanners already have tools in place for quantitative assessment of skeletal muscle blood flow, though, whereas conventional SPECT systems are limited to evaluation of relative perfusion. Therefore, both SPECT and PET possess relative benefits and limitations that should be taken into account during evaluation of extremity trauma.

SUMMARY

Along with the more established clinical imaging modalities already discussed, additional noninvasive approaches continue to emerge that could one day reach widespread application for the assessment of extremity trauma. Specifically, ultrasound systems continue to evolve and can now be incorporated with other imaging approaches such as near-infrared spectroscopy and photoacoustic imaging, thus creating hybrid systems that may lead to additional applications for ultrasound systems in the future. Additional progress in the field of ultrasound contrast agents and nanoparticles may also facilitate targeted molecular imaging for the evaluation of various regenerative medicine treatments for extremity trauma. Other modalities such as $TcPO_2$,[58] laser Doppler imaging,[59] laser speckle flowmetry,[60] and hyperspectral imaging[61] are also available and could possess potential utility in the evaluation of

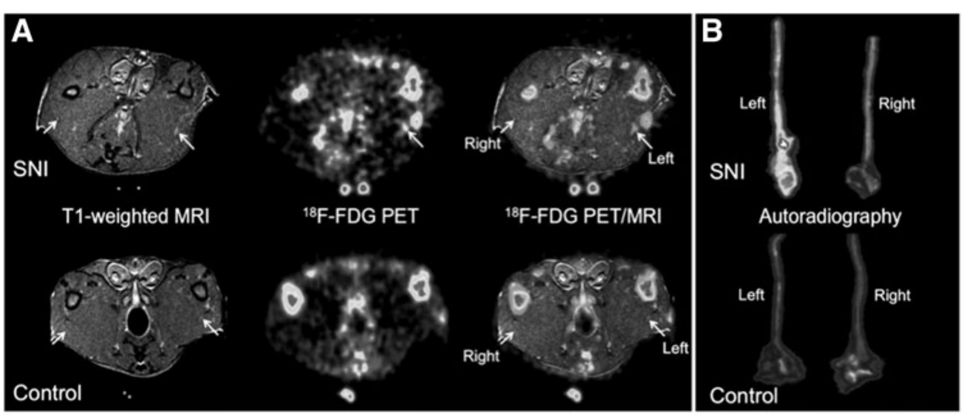


Figure 4. PET/MR imaging in a rat model of unilateral spared-nerve injury of the left sciatic nerve (**A**, *top row*) compared with a control uninjured animal (**A**, *bottom row*) demonstrates increased ^{18}F-FDG uptake in the limb (left) with nerve injury. Autoradiography of the excised sciatic nerves from injured (**B**, *top row*) and uninjured (**B**, *bottom row*) animals reveals dramatically higher radiotracer uptake in the injured (left) sciatic nerve compared with control sciatic nerves. This research was originally published in J Nucl Med.[56] © by the Society of Nuclear Medicine and Molecular Imaging, Inc. FDG, fluorodeoxyglucose; PET, positron emission tomography; SNI, spared-nerve injury.

residual limb tissue health; however, these approaches are traditionally limited by their ability to assess measures of tissue perfusion and blood flow at a superficial level and may present issues with regard to a reproducible serial assessment of specific anatomical sites due to their limited field of views.

Currently, a variety of imaging modalities are available that offer a wide range of diagnostic information on patients who have suffered extremity trauma. Although many modalities exist, all of these imaging approaches still come with relative strengths and limitations. Therefore, clinicians who are responsible for the noninvasive assessment and fast care of patients and military service members after traumatic extremity injury should give careful consideration of the pros and cons associated with each modality to facilitate and optimize evaluation and medical treatment that will lead to the most favorable clinical outcomes.

TAKE-HOME MESSAGES

- Traumatic extremity injuries are clinical problems that require fast diagnosis and treatment to facilitate limb salvage and positive patient outcomes.
- Multiple imaging modalities are available for noninvasive assessment of extremity complications after traumatic events; however, certain modalities are favored depending on the form of traumatic injury.
- Ultrasound imaging offers the ability to quickly assess real-time images of structure, function, and blood flow, but it is limited by its penetration depth.
- CT imaging offers rapid image acquisition times, excellent penetration depth, and high-spatial resolution for assessment of vascular anatomy, bone, and surrounding soft tissue. However, limitations of CT include the use of X-rays that expose patients to ionizing radiation, as well as image artifacts that can be created from metallic foreign bodies.
- MR imaging provides high-resolution images that are capable of assessing anatomy and function without the need for ionizing radiation; however, limitations of MR imaging in the assessment of traumatic extremity injuries include long image acquisition times, high cost, and its contraindication when there is the suspected presence of metallic foreign bodies from blast-related injuries.
- Radiotracer imaging with SPECT and PET offers high-sensitivity functional assessment of a wide range of physiological processes, but it is limited by poor spatial resolution that often requires the pairing of SPECT and PET with high-resolution CT or MR systems for optimal radiotracer localization and quantification.

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AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article. The views expressed in this article are those of the authors, and do not necessarily reflect the official policy of the Departments of the Army, Navy, Defense, nor the United States Government.

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Abbreviations and Acronyms

2D = two-dimensional
3D = three-dimensional
^{15}O = oxygen-15
^{18}F = fluorine-18
^{67}Ga = gallium-67
^{99m}Tc = technetium-99 m
CT = computed tomography
DSA = digital subtraction angiography
FDG = fluorodeoxyglucose
MR = magnetic resonance
DTI = diffusion tensor imaging
MDP = methyl diphosphonate
PET = positron emission tomography
SPECT = single photon emission computed tomography
$TcPO_2$ = transcutaneous oxygen

Impact of Traumatic Lower Extremity Injuries Beyond Acute Care: Movement-Based Considerations for Resultant Longer Term Secondary Health Conditions

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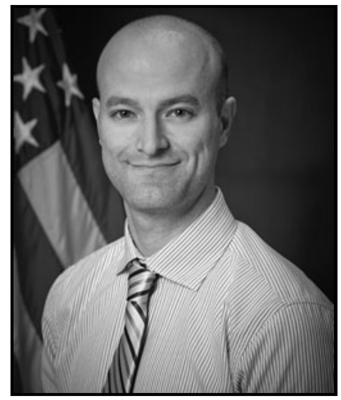

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Significance: Advances in field-based trauma care, surgical techniques, and protective equipment have collectively facilitated the survival of a historically large number of service members (SMs) following combat trauma, although many sustained significant composite tissue injuries to the extremities, including limb loss (LL) and limb salvage (LS). Beyond the acute surgical and rehabilitative efforts that focus primarily on wound care and restoring mobility, traumatic LL and LS are associated with several debilitating longer term secondary health conditions (*e.g.*, low back pain [LBP], osteoarthritis [OA], and cardiovascular disease [CVD]) that can adversely impact physical function and quality of life.

Recent Advances: Despite recent advancements in prosthetic and orthotic devices, altered movement and mechanical loading patterns have been identified among persons with LL and salvage, which are purported risk factors for the development of longer term secondary musculoskeletal conditions and may limit functional outcomes and/or concomitantly impact cardiovascular health.

Critical Issues: The increased prevalence of and risk for LBP, OA, and CVD among the relatively young cohort of SMs with LL and LS significantly impact physiological and psychological well-being, particularly over the next several decades of their lives.

Future Directions: Longitudinal studies are needed to characterize the onset, progression, and recurrence of health conditions secondary to LL and salvage. While not a focus of the current review, detailed characterization of physiological biomarkers throughout the rehabilitation process may provide additional insight into the current understanding of disease processes of the musculoskeletal and cardiovascular systems.

Keywords: amputation, biomechanics, cardiovascular disease, limb salvage, low back pain, osteoarthritis

SCOPE AND SIGNIFICANCE

Extremity trauma, including limb loss (LL) and limb salvage (LS), is commonly associated with an elevated risk for secondary health conditions (*e.g.*, low back pain [LBP], osteoarthritis [OA], cardiovascular disease [CVD]) that can significantly limit physical function, reduce quality of life (QoL), and life expectancy. This review

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provides an extensive commentary regarding resultant secondary health effects of extremity trauma in service members (SMs), with a particular focus on functional outcomes and quality of movement.

TRANSLATIONAL RELEVANCE

Physiologic biomarkers provide an opportunity to enhance translation in future work to examine the pathophysiology of the secondary health conditions associated with traumatic LL from a basic science perspective. While this approach is yet to be fully explored and thus was not a primary focus of this review, such biomarkers may augment traditional analyses and support more comprehensive risk characterization, thereby allowing clinicians and researchers to better mitigate disease onset or progression.

CLINICAL RELEVANCE

The increased prevalence of secondary health effects following traumatic extremity injuries places a significant physical and psychosocial burden on SMs with LL and LS. Altered movement patterns often result in mechanical loading of the spine and lower extremities, potentially increasing the risk of LBP and OA. Adopting a biopsychosocial model of treatment/care may allow clinicians to utilize a multifaceted approach to treat chronic pain and dysfunction associated with resultant health effects of LL.

BACKGROUND

Musculoskeletal disorders are the most prevalent source of disability in the United States.[1,2] As a result, the annual direct costs associated with treatment total a substantial $900 billion.[3] Among these, extremity amputation, or LL, is projected to affect an estimated 3.6 million people by the year 2050.[4] Approximately 185,000 individuals undergo either an upper or lower extremity amputation annually, primarily due to trauma, dysvascular disease, and/or osteosarcoma.[5–7] While the incidence of LL due to dysvascular etiologies has steadily risen among the civilian sector, trauma remains a leading source of LL within the Military Health System. However, prior estimates of the current/future impact of LL do not include SMs injured during combat nor do they consider individuals with LS; an alternative to amputation in which heroic measures are undertaken by the military surgical teams at all echelons of care to preserve as much form and function of the traumatically injured limb as possible. Despite these surgical efforts and advances in orthotic technology, many with LS are unable to achieve preinjury functional outcomes, much like those with LL.

The combat theaters of Operations: Enduring Freedom (OEF), Iraqi Freedom (OIF), New Dawn, Inherent Resolve, and Freedom's Sentinel were characterized by high-energy munitions and explosives. With advances in personal protective equipment, field-based trauma care, and surgical techniques, injuries sustained as a result of these often-improvised devices are now survivable at higher rates than conflicts past. However, traumatic extremity injuries, including LL and LS, remain a hallmark casualty of recent conflicts. Across all services, 52,351 military personnel have been wounded in action since 2001[8]; more than half of evacuated SMs have sustained extremity injuries and nearly a quarter of these are open fractures.[9] In addition, 1,703 SMs sustained injuries requiring major (or multiple) limb amputation (As of October 1, 2016; Data source: EACE-R). The decision to amputate a limb may be made in as few as 24 h post-trauma, during the first hospitalization as a secondary surgical intervention, or potentially years after LS (*i.e.*, delayed amputation).[10–13] Factors contributing to the decision include the extent and severity of injuries and resources available during the rehabilitation process.[14] Recent evidence suggests that SMs who undergo LS will typically experience more expansive complications than individuals who undergo amputation.[15–17] LS has been associated with significantly higher rates of rehospitalization, greater numbers of surgical procedures, and higher rates of surgical complications.[18,19]

Initial wound care and rehabilitation after LL and/or LS are critical to the recovery process. Such efforts are generally categorized by nine distinct phases, each with specific goals and objectives.[20] The complexity and interdependence between each phase elucidate the need for an efficient interdisciplinary approach within the overall rehabilitation paradigm. Despite these comprehensive and substantive efforts, persons with LL and LS are at an increased risk for acute secondary health conditions such as phantom limb pain, wounds/sores, vascular and nerve damage, infection, decreased physical function, and psychosocial issues. Furthermore, beyond these acute conditions, persons with LL and LS are also at an elevated risk for longer term complications including LBP, OA, and CVD, among others. Importantly, once the disease progression initiates, these longer term resultant conditions will plague these individuals for life, as SMs with extremity trauma are typically younger than 30 years at the time of

injury and thus will continue living with their injuries for several decades.[17]

The long-term economic burden of trauma-related LL and LS is significant. Edwards *et al.* predicted the long-term (40 year) cost of trauma repair, rehabilitation, and lifelong prosthetic support of British soldiers wounded in Afghanistan to be approximately \$444 million.[21] In the United States, the estimated average lifetime cost of treatment for unilateral lower LL is \$342,716 and \$1.4 million for Vietnam and OIF/OEF veterans, respectively.[22] However, such estimates are likely conservative, not fully accounting for costs associated with novel technology/repairs or, perhaps exponentially more economically burdensome over the longer term, for the wide range of healthcare costs associated with the treatment of secondary health conditions. The ability to evaluate, predict, and ultimately treat these resultant health conditions would not only help reduce these costs but also, and most importantly, preserve and/or improve function and QoL for those with LL and LS.

The risk for secondary health conditions is often related to physiological adaptations to trauma or pervasive surgical complications, poor biomechanics, and/or the prosthetic (orthotic) device itself. For SMs, in particular, the young age at which these injuries occur likely presents a unique challenge over the longer term and further highlights the importance for understanding resultant health conditions secondary to extremity trauma. Notably, the cumulative effects of many years of functional adaptations during gait and movement with extended prosthetic/orthotic device use in otherwise young and active SMs remain unclear.[23,24] This is an important distinction from civilian populations as a majority of civilians with LL are over the age of 50, incurred LL as a result of vascular damage/complications, are likely less active, and may present with different resultant health conditions/outcomes for less time.[25] Thus, as a preliminary step toward addressing this knowledge gap, the purpose of this review is to provide a commentary regarding resultant health conditions associated with high-energy extremity trauma, with a primary focus on biomechanical features of movement and associated functional limitations. In particular, we highlight considerations for longitudinal care aimed at maximizing QoL, for those with both LL and LS.

DISCUSSION

Low back pain

The World Health Organization describes LBP as any pain or discomfort for a variable duration in the lumbar spine region.[26] The onset of pain may occur suddenly, coincident to a singular traumatic event, or develop over time with age or as the result of repeated microtrauma from a given (or set of) activity(ies). Often, LBP is considered idiopathic, as pain may be present without pathoanatomical evidence of disease or structural abnormality. LBP costs nearly \$100 billion annually in the United States, with a majority of this cost associated with lost wages and decreased productivity.[27] While cross-sectional figures indicate that chronic LBP affects up to 33% of adults in the general population, the incidence in persons with LL who report LBP secondary to trauma is nearly double (52–76%).[28–31] Along with this significantly higher prevalence, nearly 50% of persons with LL have reported LBP as "more bothersome" than either residual or phantom limb pain and as having a significant reduction in overall QoL metrics.[28,30,32] While the exact etiology of LBP within this population is unclear, there is a growing body of evidence suggesting that altered lumbopelvic mechanics during the (repetitive) gait cycle likely influences such risk.

Persons with lower LL frequently develop altered movement patterns to maintain balance and achieve forward progression in walking. Movement patterns can be influenced by the following, either individually or in combination: socket fit/prosthetic alignment, general deconditioning, leg length discrepancies, complications within the residual limb, and muscular imbalances.[33,34] More specifically, altered movement patterns during gait affect trunk and pelvis mechanics and contribute, at least in part, to the increased incidence of LBP in persons with lower LL and may be dependent on the extent of injury or ultimate level of amputation.[35–38] These alterations and asymmetries may increase loads on the lumbar spine during gait which, when considering the repetitive gait cycle, over time may thus contribute to the occurrence or recurrence of LBP. For example, persons with transfemoral LL tend to exhibit 10° of anterior pelvic tilt, which is considered to be a compensatory mechanism to assist in the ability to achieve hip extension during gait. Increased anterior pelvic tilt is associated with increased lumbar lordosis, which is linked to an increased incidence of LBP in persons with LL.[28,39] Previous work has demonstrated that increased loads on the lumbar spine are a direct source of LBP in the general population.[40,41] Mechanical loading of the passive and active structures of the spine is affected by both internal and external loads, such as forces produced by muscular activation, ligamentous tension, gravity, and inertia.[42]

These loads can be significant, as potentially small alterations in trunk (which accounts for nearly 2/3 of the body's mass) movement may increase joint reaction loading due to increased muscular contractions of the surrounding musculature.[43] The increased demand on the active structures (muscles) may lead to increased forces and joint loading on the passive structures (discs and vertebrae). The accumulation of these altered loads over time has the potential to augment degenerative joint changes in the spine.[40]

Similar to uninjured individuals with LBP, persons with transfemoral LL exhibit irregular trunk–pelvis coordination and movement variability.[44] Specifically, persons with LL tend to walk with a large lateral trunk lean toward the affected side; a possible neuromuscular strategy/compensation to assist in forward progression during gait.[42] This frontal plane motion has been reported to increase peak joint reaction forces and moments asymmetrically in the lumbar spine (L5-S1 integration specifically) in this population. A recent report suggested this observed frontal plane motion as a possible mechanistic pathway through which recurring exposure to altered trunk motion and cumulative spinal loading may contribute to LBP in persons with lower LL.[42] Persons with transfemoral LL (with current LBP) exhibit larger axial trunk rotations when compared to those without LBP, which may subsequently affect vertebral disc degeneration and potentially contribute to LBP recurrence.[45,46] Previous evidence demonstrated degenerative changes in the lumbar spine via radiographic imaging in 76% of persons with LL, potentially supporting the role of increased trunk motion leading to degenerative changes in this population.[47]

While LBP is commonly cited as a secondary health effect of LL, persons with LS may also experience LBP as a result of altered movement patterns during gait and functional activities.[48] Persons with LS typically experience reduced ankle function, which is associated with altered gait mechanics and increased metabolic cost.[34,49,50] However, the influence of distal LS on proximal (trunk/pelvis) biomechanics remains unstudied to date. Currently, a paucity of evidence exists relative to the prevalence of LBP in the LS population. Therefore, further work is needed to elucidate the relationship between LS and the development of LBP.

In summary, LBP has been reported as the most important health-related physical condition contributing to a reduced QoL among veterans who had sustained a traumatic lower extremity amputation over 20 years prior.[32] Thus, identifying factors contributing to the development and recurrence of LBP, such as a widely prevalent and "bothersome" secondary health concern, is critical for improving long-term health. Abnormal mechanical loading of lumbar spine, altered trunk and pelvis coordination, and psychosocial factors may influence the prevalence of LBP in this population. Therapeutic interventions that address the underlying impairment(s) in trunk neuromuscular responses and/or motor control strategy may also contribute to reducing the prevalence and incidence of LBP among SMs with lower extremity trauma, thereby improving longer term functional outcomes by mitigating a significant secondary impairment with a substantial adverse impact on daily activities. Further evidence is needed to understand the relationship between these risk factors and the incidence of LBP in persons with LL. In particular, no studies to date have evaluated the influence of different prostheses or orthoses on the incidence of LBP in the traumatic LL and LS populations.

Osteoarthritis

The National Institute of Arthritis and Musculoskeletal and Skin Diseases describes OA as a joint disease affecting the cartilage, often characterized by pain and stiffness within a joint and limitations in physical function.[51] The primary pathology is articular cartilage deterioration, although evidence suggests that possible morphological changes of bone are reflective of disease onset. Within the joint, articular cartilage functions to dissipate forces sustained by the bony structures throughout motion. During activities such as walking or running, when the loading velocity and intensity of the structures are increased, the cartilage's ability to dissipate forces is reduced.[52] In the general population, mechanical loading of the knee joint during walking has been associated with the presence, severity, and progression of knee OA.[53–56] Persons with unilateral lower LL are 17 times more likely to suffer from knee OA in the intact limb when compared to able-bodied individuals.[57]

As previously noted, persons with LL frequently develop altered movement patterns during gait. Of particular importance here, those with unilateral LL preferentially utilize their intact limb, leading to increased and prolonged loading of the intact joints. Mechanical alterations in static and dynamic alignment of the knee joint may affect joint loading as increased forces are incurred through medial or lateral aspects of the joint. The external knee adduction moment (EKAM) is a vastly reported risk factor for knee OA based on its relationship with internal loading of the medial joint surface.[58] The size of the EKAM and its respective angular impulse

are associated with knee OA severity and progression.[53,55,59,60] During gait, individuals with lower LL asymmetrically load their intact limb to a greater extent than their involved limb, suggesting that mechanical factors play a role in the increased incidence of knee OA in this population.[36,61] For example, Lloyd *et al.* identified larger peak knee adduction moments in the intact relative to involved limb.[62] This increased mechanical loading may be explained by decreased push-off power and ground reaction forces demonstrated with conventional prosthetic feet.[61,63] Push-off power generated by the prosthetic foot instance may affect the ground reaction forces at heel strike in the intact limb as the velocity of an individual's center of mass changes from an anterior and inferior direction to an anterior and superior direction during gait.[64] The redirection of the center of mass is caused by the ground reaction impulse through the gait cycle, crudely relative to double-limb support.[64] If the prosthetic stance foot lacks adequate push-off power to propel the center of mass anteriorly, the intact limb must compensate by performing more work to move the center of mass anterior and superior, resulting in increased ground reaction forces and loading of the intact limb.[61] Morgenroth *et al.* suggested that by utilizing a prosthetic foot with increased push-off power, the peak EKAM of the intact limb may be reduced and therefore potentially decreasing the OA risk.[61] This was supported as a powered ankle–foot prosthetic was able to decrease the EKAM and vertical ground reaction force in persons with lower LL, however, the prosthetic used was unable to alter the knee joint loads of the intact limb.[65] Similar to LBP, the progression and severity of OA may be further amplified by psychosocial determinants; anxiety, depression, coping strategies, and stress have also been associated with increased pain in patients with OA.[66–68]

OA is not exclusive to the LL population as individuals with LS present with similar (sometimes larger) gait and movement deviations. As high as 95% of OA diagnoses among combat-wounded SMs are post-traumatic in origin.[69] Chronic pain, nerve damage, and volumetric muscle loss are common barriers to LS rehabilitation and may serve as confounding factors in the development of OA treatment plans.[70,71] Ankle–foot orthoses (AFOs) are commonly used to assist ankle function or offload painful structures.[72] Optional therapies that include sports medicine-based interventions utilizing a dynamic AFO (*e.g.*, the Intrepid Dynamic Exoskeletal Orthosis) are available to LS patients. Such devices are designed to improve functional performance on tasks such as walking, changing directions, sit-to-stand, and ascending stairs.[48] While dynamic AFOs are suggested to improve functional capabilities, evidence is inconclusive in its ability to positively alter gait parameters related to OA as well as the effects of long-term use.[34,73,74]

Treatment modalities focused on reducing symptoms and OA disease progression in persons with LL and LS are vital to improving QoL. The Osteoarthritis Research Society International recommends biomechanical interventions, intra-articular corticosteroids, exercise (land and water based), self-management and education, strength training, and weight management.[75] Autologous platelet-rich plasma (PRP) therapy is a therapeutic intervention that delivers high concentrations of growth factors to an area to stimulate healing.[76] Recent evidence suggests that PRP may provide relief of knee OA symptoms in younger patients within the early stages of cartilage degeneration.[77–79] Strength training (weight and body-weight training) and exercises such as t'ai chi have demonstrated the ability to improve overall function in decreasing pain in OA patients and may also serve to assist in weight management.[80,81] Weight reduction is considered a pragmatic therapy for knee OA as overweight individuals demonstrate a high prevalence of knee OA and the risk of severity progression increases 35% for every 5 kg of weight gain.[82] Strength training and weight management are considered integral aspects of the rehabilitation paradigm for persons with LL as deficits in strength and increases in weight influence gait, joint loading, movement efficiency, and cardiovascular health. Canes, knee braces, and foot orthotics are other potential treatment options to decrease movements at the knee, reduce pain, and improve function.[83–85]

In summary, biomechanical factors likely play a substantial role in the risk for OA secondary to extremity trauma, whether LL or LS. While the prevalence of OA in LL and LS populations may decrease as technological improvements in prostheses and orthoses are realized, further evidence is needed to determine the specific relationship between different classes or features of these devices and OA risk factors. Unfortunately, recent technological advancements in prosthetic devices have outpaced orthotic devices, the benefits of which are evident in the biomechanical characteristics of persons with LL versus LS. Nevertheless, LS typically presents with more complex neurovascular injuries and other unique challenges, which can negatively affect functional outcomes.

Cardiovascular disease

CVD is defined by a vast array of diseases affecting the heart and blood vessels.[86] CVD may present

as coronary artery disease, stroke, arrhythmias, cardiomyopathy, heart disease, peripheral artery disease, aneurysms, venous thrombosis, and/or carditis.[86,87] While CVD is largely preventable, it remains the leading cause of death worldwide, particularly in lower socioeconomic demographics.[86] The American Heart Association reports there are ~85 million individuals with CVD in the United States, causing a staggering 2,200 deaths each and every day.[88] This is accompanied by direct and indirect costs of nearly $315 billion.[89] Risk factors for CVD include, but are not limited to, family history and genetics, high cholesterol and lipids, high blood pressure, diabetes, metabolic syndrome, obesity, and kidney disease.[89] In addition, significant combat trauma may be a risk factor for the development of CVD.[90–92] For example, Hrubec and Ryder conducted a 30-year follow-up of World War II veterans with lower LL and demonstrated that the relative risk of CVD mortality was increased 2.4–4 times that of persons with LS.[90] Similarly, Modan *et al.* reported significantly higher mortality rates of persons with traumatic lower LL when compared to able-bodied controls, suggesting that CVD was the primary cause (21.9% vs. 12.1%, $p < 0.001$).[91]

The pathophysiology of increased mortality rates may be a result of systemic and/or regional hemodynamic effects of trauma.[91,93–97] Obesity and hypertension secondary to decreased overall activity levels may lead to insulin regulation complications in persons with LL.[97] When compared to uninjured controls with no difference in body mass index, blood pressure, or lipid levels, persons with LL exhibited significantly higher increased fasting plasma insulin levels as well as insulin resistance.[96] Increased plasma insulin levels and insulin resistance are risk factors for atherosclerosis and metabolic syndrome, considered precursors to CVD. The role of psychological stressors in the development of CVD is not well understood; however, psychosocial factors have demonstrated involvement in the pathogenesis of CVD.[98,99] Depression and post-traumatic stress disorder have been associated with increased incidence of CVD, while veterans with high levels of cynical distrust and anger demonstrate an accelerated progression of atherosclerosis, a risk factor for CVD.[100–102] Limited evidence precludes a definitive relationship between psychosocial factors and CVD risk in persons with LL, and therefore, future work should prospectively examine the relationship between psychosocial factors/stressors and the development of CVD.

Hemodynamically, proximal amputation increases the risk of CVD development based on alterations in proximal arterial flow. Pathogenic mechanisms may include early reflection pulse waves. Early return reflection pulse waves are produced at arterial occlusion sites and have been linked to a myriad of medical complications.[103] An early returned reflection pulse wave creates a second systolic peak, which results in an increase in aortic pressure. The increased aortic pressure generates an increased left ventricular load resulting in left ventricular hypertrophy, atherothrombosis, and ultimately cardiac death.[104] Vollmar *et al.* suggested that persons with traumatic LL above the knee were five times more likely to suffer from abdominal aortic aneurysms when compared to healthy controls.[94] A possible explanation may be that after amputation, blood flow is decreased by ~25% in the terminal aorta due to altered flow paths in the visceral and renal arteries, resulting in a disrupted flow pattern at the aortic bifurcation.[95] Altered flow patterns, paired with increased shear stress along the convex aspect of the aorta and decreased shear stress along the concave aspect, are theorized to damage aorto-iliac blood vessels by increasing hydraulic forces within the aorta.[95] Persons with transfemoral LL should have regular consultations with appropriate medical personnel to assess the risk of abdominal aortic aneurysm.[95]

While the hemodynamic effects of trauma appear to influence CVD risk, addressing modifiable risk factors may be an effective strategy to help decrease CVD risk. It is widely accepted that habitual exercise with activities such as running, walking, bicycling, rowing, and swimming increases aerobic capacity and decreases the risk of CVD. When joined with dietary modifications, regular exercise can effectively reduce excess body weight, another risk factor for CVD. Moreover, the increased risk of CVD in persons with LL highlights the importance of managing modifiable risk factors, engaging in preventative treatment strategies, and adopting an active lifestyle.

SUMMARY

Maintaining an active lifestyle is critically important for physiological health, psychological well-being, and overall QoL. Such guidance is no different for individuals with LL and LS. However, given the limited (but growing) body of evidence relating movement abnormalities to altered musculoskeletal demands that may lead to the development of longer term secondary conditions in this population, additional consideration for the quality of movement during recreational and daily activities is warranted. While the overwhelming focus of recent efforts has been on persons with LL, the aforementioned secondary health conditions are likely also major con-

cerns for those with LS. As such, we posit that an underlying focus of clinical care and future research, in both cohorts, should be toward mitigating concomitant risk for the development or recurrence of chronic pain.

While advances in trauma care and prosthetic/orthotic technologies may eventually mollify acute and subacute secondary health effects of extremity trauma, longitudinal tracking is urgently needed to better understand the mechanisms by which secondary health effects develop and progress in this population. Such efforts should encompass a transdisciplinary team, in which a comprehensive suite of evaluation metrics are employed; for example, traditional clinical evaluation and movement analysis supplemented with local and systemic physiological biomarker analyses and next-generation imaging modalities. In doing so, a better understanding of the specific pathways for the development of these secondary health effects can be realized, thus enabling clinicians to develop and prescribe appropriate treatment interventions. Ultimately, diminishing risk factors relative to the degeneration of joint and cardiovascular function will reduce the overall prevalence of secondary health conditions and improve QoL for our nation's injured SMs and veterans over the longer term.

TAKE-HOME MESSAGES

- Living with LL and LS over time leads to increased morbidity and mortality from secondary medical and musculoskeletal problems. Awareness of the long-term health risks associated with LL and LS, as well as the physiologic and biomechanical origin of these risks, is critical to improving outcomes
- Understanding the pathogenesis of the secondary health conditions of traumatic LL and LS and salvage may help guide optimal management in acute, subacute, and chronic phases of care for these individuals
- Reducing modifiable risk factors through patient education, identifying appropriate support systems, encouraging proper gait mechanics, and utilizing the prescription of evolving technologies may help mitigate long-term health conditions

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No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article. The views expressed in this article are those of the authors and do not necessarily reflect the official policy of the Departments of the Army, Navy, Defense, nor the United States Government.

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Abbreviations and Acronyms

AFO = ankle–foot orthoses
CVD = cardiovascular disease
EACE = Extremity Trauma and Amputation Center of Excellence
EKAM = external knee adduction moment
LBP = low back pain
LL = limb loss
LS = limb salvage
OA = osteoarthritis
OEF = Operation Enduring Freedom
OIF = Operation Iraqi Freedom
PRP = platelet-rich plasma
QoL = quality of life
SM = service member
USUHS = Uniformed Services University of the Health Sciences
WRNMMC = Walter Reed National Military Medical Center

Evaluating Traumatic Extremity Injuries Using Multimodality Imaging: Emphasis on SPECT/CT Imaging and Implications for Military Medicine

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INTRODUCTION: Service members (SM) injured during combat can suffer complex traumatic extremity injuries, including limb loss (LL). The health of residual limb tissue in individuals with LL is of critical importance. Breakdown of tissue viability of the residual limb can negatively impact the progress of the patient's rehabilitation and/or lead to prosthesis abandonment, thus reducing their mobility, function, and overall quality of life. Therefore, effective diagnosis of tissue viability is critical in directing the medical treatment of patients. Multimodality imaging approaches offer a non-invasive, sensitive, and quantitative means by which to assess tissue viability. This abstract reviews current multimodality clinical imaging approaches, with special attention to single photon emission computed tomography (SPECT)/CT imaging, which may have particular relevance for evaluating residual limb health of patients with traumatic LL.

METHODS: A literature review was conducted to evaluate the effectiveness of non-invasive imaging modalities, such as ultrasound, X-ray CT imaging, magnetic resonance (MR) imaging, SPECT/CT, and positron emission tomography (PET), at assessing various anatomical and physiological aspects of residual limb health. The relative benefits and limitations of each modality are presented herein, with a particular focus on SPECT/CT perfusion imaging.

RESULTS: A variety of imaging modalities are available that offer a wide range of diagnostic information on patients who have suffered extremity trauma. Each of these imaging modalities possesses relative benefits and limitations in their ability to provide a comprehensive non-invasive assessment of the anatomical and physiological health of the residual limb (Table 1). Recently, there has been an increased focus on the development of non-invasive imaging approaches capable of assessing tissue viability in patients with LL. Radiotracer-based imaging with SPECT/CT offers a quantitative assessment of bulk tissue perfusion within three-dimensional regions of interest under resting conditions or in response to exercise or pharmacological stress, thereby providing potential insight into sensitive changes in tissue viability within residual limbs. Our initial application of SPECT/CT imaging has demonstrated sensitivity for identifying deficits in microvascular perfusion in patients with non-healing lower extremity wounds while also allowing for evaluation of responses to medical treatment.

Table 1. *Characteristics of imaging modalities available for assessing extremity trauma*

Modality	*Sensitivity*	*Penetration Depth*	*Spatial Resolution*
Ultrasound	Moderate	Low	1 mm
CT imaging	Limited	No limit	<1 mm^3
MR imaging	Moderate	No limit	<1–3 mm^3
SPECT	High	No limit	$\sim$5–8 mm^3
PET	High	No limit	$\sim$3–5 mm^3

Modified from Stacy and Sinusas.[7]
CT, computed tomography; MR, magnetic resonance; PET, positron emission tomography; SPECT, single photon emission computed tomography.

DISCUSSION: The ability to utilize quantitative imaging approaches that assess tissue viability through the evaluation of vascular supply, tissue blood flow, perfusion, and/or oxygenation within residual limbs could provide novel insight into physiological changes that occur within the residual limb of SM with LL following surgical or medical treatment. This will also allow for improved assessment of next generation prosthetic devices. Evidence suggests that SPECT/CT offers a promising method by which to accomplish these goals. To expand on the extant literature, a pilot clinical study is currently underway at WRNMMC to translate SPECT/CT perfusion imaging to patients with LL to assess its effectiveness at evaluating the impact of next-generation socket technologies on the health of the residual limb, thereby benefiting patient care.

Evaluating Traumatic Extremity Injuries Using Multimodality Imaging: Emphasis on SPECT/CT Imaging and Implications for Military Medicine

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BACKGROUND

- Service members (SM) injured during combat can suffer complex traumatic extremity injuries, including limb loss (LL).
- The health of residual limb tissue in individuals with LL is of critical importance. Breakdown of tissue viability of the residual limb can negatively impact the progress of the patient's rehabilitation and/or lead to prosthesis abandonment, thus reducing their mobility, function, and overall quality of life.
- Effective diagnosis of tissue viability is critical in directing the medical treatment of patients. Multimodality imaging approaches offer a non-invasive, sensitive, and quantitative means by which to assess tissue viability.
- Each imaging modality possesses relative benefits and limitations in their ability to provide a comprehensive non-invasive assessment of the anatomical and physiological health of the residual limb (Table 1).

Table 1. Imaging modalities available for assessing extremity trauma

Modality	Sensitivity	Penetration Depth	Spatial Resolution
Ultrasound	Moderate	Low	1 mm
CT Imaging	Limited	No Limit	< 1 mm^3
MR Imaging	Moderate	No Limit	< 1-3 mm^3
SPECT	High	No Limit	~3-5 mm^3
PET	High	No Limit	~3-5 mm^3

Modified from Stacy MR et al. Curr Pathobiol Rep. 2015;3(1):27-38.

- Recently, there has been an increased focus on the development of non-invasive imaging approaches capable of assessing tissue viability in patients with LL.
- Radiotracer-based imaging with single photon emission computed tomography (SPECT)/CT offers quantitative assessment of bulk tissue perfusion within three-dimensional regions of interest under resting conditions or in response to exercise or pharmacological stress, thereby providing potential insight into sensitive changes in tissue viability within residual limbs.
- Our initial application of SPECT/CT imaging, presented herein, demonstrates sensitivity for identifying deficits in microvascular perfusion in the lower extremities and may offer a novel non-invasive approach for evaluating patients with LL who are receiving next-generation prosthetic devices.

METHODS

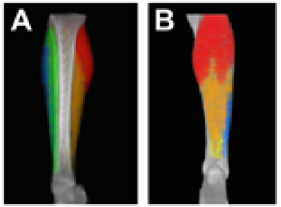

Figure 1. Volume rendered muscle groups of the calf overlaid on CT images. A) Anterior and B) posterior views display the segmented gastrocnemius (red), soleus (orange), tibialis anterior (green), tibialis posterior (yellow), and peroneus longus (blue) muscles.

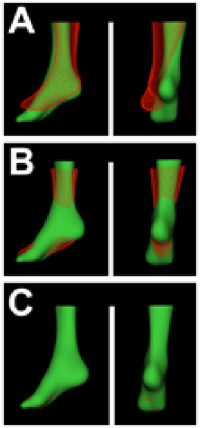

Figure 2. Serial registration of CT images of the lower extremities to correct for movement or change in position of limb between pre- and post-treatment study visits. Image registration was performed using points from outer skin surfaces. Shown are rendered surfaces from two separate study visits (red = visit 1; green = visit 2) at the (A) starting position before registration, (B) after global rigid alignment, and (C) after non-rigid registration.

SPECT/CT IMAGING APPLICATIONS

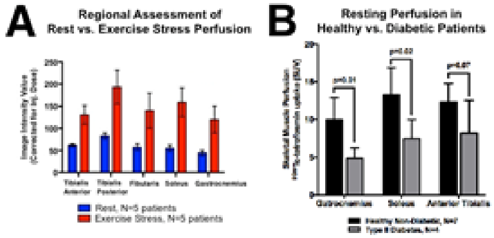

Figure 3. SPECT/CT imaging allows for regional assessment of stress-induced changes in skeletal muscle perfusion and identifies regional differences in resting perfusion of the lower extremities between healthy and diabetic patients. A) Exercise stress-induced changes in perfusion are characterized within specific muscle groups of the lower extremity in healthy patients. B) SPECT/CT imaging under resting conditions reveals significant differences in regional skeletal muscle perfusion between healthy and diabetic patients.

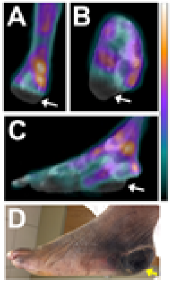

Figure 4. Resting ^{99m}Tc-tetrofosmin SPECT/CT perfusion imaging in a patient with a non-healing foot ulcer. A) Coronal, (B) axial, and (C) sagittal views of fused SPECT/CT images reveal a relative perfusion defect (denoted by white arrows) located in the (D) region of to the non-healing wound (denoted by yellow arrow) that extends along the plantar aspect of the foot.

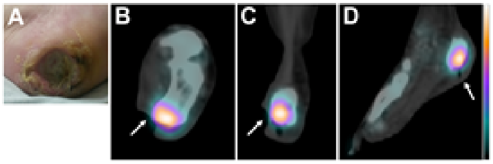

Figure 5. ^{99m}Tc-methylene diphosphonate (MDP) SPECT/CT imaging of osteomyelitis in a lower extremity wound. A) A patient presenting with a deep non-healing heel wound. B) Axial, C) coronal, and D) sagittal views of ^{99m}Tc-MDP SPECT/CT imaging of the foot revealed the presence of osteomyelitis localized to the wound site.

SPECT/CT IMAGING APPLICATIONS

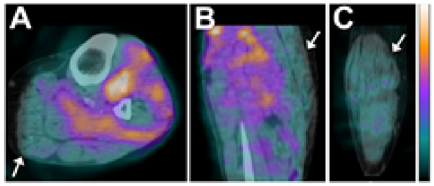

Figure 6. SPECT/CT perfusion imaging of the calf under resting conditions. A) Axial, B) sagittal, and C) coronal views of fused SPECT/CT images reveal a regional perfusion deficit in the gastrocnemius muscle (denoted by white arrows).

SUMMARY

- Abnormalities in lower extremity tissue perfusion can be non-invasively detected in the calf or foot under rest or stress conditions by utilizing SPECT/CT imaging.
- SPECT/CT perfusion imaging, in combination with other physiological radiotracer-based imaging, may offer novel insight into the tissue viability of residual limbs while also allowing for assessment of the physiological changes that occur following implementation of next-generation prosthetic devices in patients with prior amputation.

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American Heart Association. life is why
NIH National Heart, Lung, and Blood Institute
CDMRP Department of Defense
EACE Extremity Trauma and Amputation Center of Excellence

Disclosures

The authors have no conflicts of interest to disclose. The opinions, interpretations, conclusions and recommendations expressed herein are those of the authors and do not necessarily reflect the official policy or position of the of the Department of the Army, Department of Defense, nor the U.S. Government.